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CLINICAL USES AND HAZARDS OF ADRENAL STEROIDS AND THEIR ANALOGUES IN THE MANAGEMENT OF RHEUMATIC DISEASES*

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INTRODUCTION

WHEN it became evident that of the thirty crystalline steroids isolated from the adrenal cortex, only hydrocortisone and cortisone possessed significant anti-inflammatory and anti-rheumatic properties, efforts were made to synthesize analogues of these two 11-oxygenated corticoids. The goal has been to find a related steroid of enhanced anti-inflammatory potency that would be free of the deleterious metabolic and clinical effects encountered in the use of the naturally-occurring hormones. This proved to be an exacting task since there is an exquisite relationship between the chemical structure and biological activity of this family of steroids. The first derivative that aroused interest when tested clinically was 9 alpha-fluorohydrocortisone which resulted from the substitution of a fluorine for a hydrogen atom at carbon 9 in the

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nucleus of the hydrocortisone molecule.[1] It was soon discovered, however, that whereas the antiphlogistic potency of this analogue when given to patients with rheumatoid arthritis was approximately ten times greater than hydrocortisone, the sodium retaining effects were of even greater magnitude, sufficient to preclude the clinical use of this steroid in the rheumatic diseases.[2] When the cortisone or hydrocortisone molecule was dehydrogenated at carbons one and two, prednisone and prednisolone were obtained. These analogues when tested in patients with rheumatoid arthritis,[3] systemic lupus erythematosus[4] and diffuse scleroderma[5] were found to be four times more potent than the parent steroids in anti-inflammatory activity and were free of sodium and water retention or potassium loss at doses required to control symptoms. In an effort to further enhance the antiphlogistic potency of prednisolone, a fluorine atom was added to carbon 9. Again, as with the first halogenated steroid, the severe loss of potassium and retention of sodium that resulted from administration of delta-1, 9 alpha-fluoro-hydrocortisone defeated its usefulness as an antirheumatic agent.[6] Other new synthetic derivatives are being tested at present and the results will be awaited with interest.

Biosynthesis, Metabolism and Disposition of Hydrocortisone in Man

The principal corticoid produced by the human adrenal cortex is hydrocortisone. Utilizing carbon 14 labeled hydrocortisone, it has been possible to measure directly the pool of hydrocortisone in the human body and the rate at which endogenous hydrocortisone is synthesized. Peterson and Wyngaarden[7] have recently determined that in normal subjects the adrenal cortices produce an average of 22 mg. of hydrocortisone daily. Upon maximal stimulation by exogenous corticotropin, it was found that endogenous production increased sevenfold to 154 mg. daily. There is a diurnal variation in the rate of hydrocortisone secretion. In one normal subject, for example, it was 1.22 mg. per hour at 9:00 a.m. and 0.51 mg. at 9:00 p.m. The corresponding plasma levels of hydrocortisone were 14 and 4 micrograms per cent. Diurnal rhythm in plasma levels and urinary excretion of corticosteroids have been reported by others.[8-11]

Following oral administration of hydrocortisone to fasting normal subjects, peak plasma levels are obtained in one to two hours. The maximal plasma concentration is related to the size of the dose admin-

istered in a ratio of approximately one microgram per cent in plasma for each milligram ingested. The plasma concentration returns to normal levels within 8 to 12 hours. The rate of disappearance of hydrocortisone from plasma is proportional to concentration; the biological half-life is approximately two hours. The major route of excretion is renal; 80 per cent of administered steroid is excreted in the urine within the first 24 hours and an additional 10 per cent in the next 48 hours. Only one per cent of the steroid excreted in the urine is unchanged; the rest is conjugated or otherwise altered by the liver.[9-12]

Benefits and Limitations of Steroids in General

The 11-oxygenated steroids discussed above—both naturally-occurring and synthetic—share certain properties and important limitations in common. All inhibit pituitary secretion of corticotropin and induce exogenous hyperadreno-corticalism. Suppression of endogenous corticotropin is of value in certain diseases such as congenital adrenal hyperplasia (adrenal virilism) or carcinoma of the breast or prostate, but it is of no significant advantage to the patient with rheumatic disease. Administration of these steroids is followed promptly by suppression of inflammation and abatement of most of the severe disabling manifestations—both systemic and local—of the various rheumatic diseases. But the disease process is not eradicated and indeed certain destructive lesions continue to progress even while adequate daily doses of steroid and apparent clinical improvement are maintained. The initial response to these agents in properly selected cases is uniformly impressive but in a considerable proportion of patients improvement declines as administration is prolonged beyond 6 to 12 months. When steroid therapy is discontinued relapse follows unless a spontaneous remission has occurred. When steroid therapy is interrupted, severe withdrawal symptoms are likely to follow and some patients may find it impossible to tolerate complete discontinuance.

Yet, despite their limitations, the 11-oxygenated steroids have proven to be of great value in the treatment of certain rheumatic diseases and have saved or prolonged the life of many patients. Today they are "drugs of choice" for patients critically ill with systemic lupus erythematosus, polyarteritis nodosa or dermatomyositis.

Evaluation of Steroid Therapy

It is difficult to critically appraise a therapeutic agent in a disease

such as rheumatoid arthritis, for several reasons. It is well known that remissions may occur spontaneously. In carefully studied groups, the remission rate varied from 13 per cent in one series[13] to 32 per cent in another[14] when aspirin was the principal medication employed and neither gold compounds nor steroids were used. Furthermore, results of treatment with any agent may be seriously biased by the very nature of the composition of the series studied. The outcome may be affected significantly by such factors as duration and severity of the arthritis, presence of irreversible changes, or age distribution of patients. The therapeutic response may be influenced by the use of supplementary drugs or other measures, by the competence of total care and by skill of management of the patients.

To control many of these factors a carefully designed and statistically valid study has been reported recently in England by a committee of the Medical Research Council and the Nuffield Foundation.[15] Sixty-one patients were allocated at random to treatment with either cortisone (30 cases) or aspirin (31 cases). Therapy was instituted while the patients were within the first year of disease and was continued for two years. The two treatment groups were especially well matched. At the end of two years, the results were remarkably similar and it was concluded that there was "little to choose between cortisone and aspirin." In another British control study of 25 children with juvenile rheumatoid arthritis treated alternately with aspirin or cortisone, the same conclusion was drawn.[16] Although these results are impressive and statistically valid they do not indicate that cortisone has no place in the treatment of rheumatoid arthritis. It would seem to us that when it is found that one of two anti-rheumatic drugs tested is not uniformly effective, then it would not be unreasonable to expect that the other drug might be beneficial in those cases that have failed to improve with the first drug. In fact, it has been observed repeatedly by other workers and ourselves that a proportion of patients with rheumatoid arthritis who failed to respond satisfactorily to aspirin (given in adequate dosage), when subsequently treated with steroid alone, showed moderate or even marked improvement that could be sustained for several years. Conversely, in some cases the arthritis was controlled better with large doses of aspirin than with restricted doses of cortisone. In a third and large group of cases that had not been satisfactorily controlled by cortisone alone, the degree of improvement was enhanced by supplementing therapy with salicylates.

Judicious Selection of Patients and Steroids

It is prudent to institute hormonal therapy only when less toxic antirheumatic agents have failed after adequate trial. The expected beneficial results from steroid therapy and the hazard of withholding treatment should outweigh the risk of serious adverse effects. In estimating expected results it should be recognized that in each of the rheumatic diseases there may occur advanced structural changes that cannot be reversed by steroid therapy.

The decision to institute steroid therapy should be seriously reconsidered when a careful pre-treatment study of the case reveals the presence of tuberculosis, psychosis or severe psychoneurosis, active peptic ulcer, severe microbial infection that cannot be readily controlled by antibiotics, diabetes mellitus, thromboembolic phenomena, severe osteoporosis or convulsive disorders.

It has been our experience and that of other observers[17, 18] that appearance, activation, and hemorrhage or perforation of peptic ulcers are more likely to occur with prednisone or prednisolone than with cortisone or hydrocortisone. The same appears to be true for compressed fractures of vertebrae. On the other hand, the incidence of sodium and water retention, potassium depletion or congestive heart failure is decidedly higher with the older than the newer steroids. Advantage should be taken of differences in potential hazards of the several steroids in choosing the most appropriate steroid for patients who manifest a predilection to any of these complications. The drug as well as the patient may now be judiciously selected.

General Principles of Dosage

The risk of deleterious side-effects increases with the size of dose prescribed. When satisfactory improvement cannot be achieved with a daily maintenance dose of approximately 50 mg. of cortisone or 15 mg. of prednisone and these doses are exceeded, it is much more likely that major undesirable side-effects will be encountered during or soon after prolonged administration. In an effort to reduce the daily dose to the lowest tolerable level, it may be necessary to urge the patient to accept less than maximal improvement, to shorten the interval between divided doses without increasing the total daily amount, or to supplement steroids with salicylates or—in cases of systemic lupus erythematosus—with antimalarial drugs.[19, 20] Women, particularly those at or

near menopause, do not tolerate adrenal steroids as well as men, and children not as well as adults. The dose should therefore be regulated accordingly.

There is little or no advantage to be gained in combining different compounds such as salicylates or tranquilizing drugs with very small amounts of steroids in a single tablet. There are several objections to such a measure. It tends to exaggerate the safety of steroid administration and impart to the patient and physician an unwarranted sense of optimism concerning the development of adverse effects. It promotes a reckless increase in the number of disorders (many of them benign and self-limited) for which these potent hormones are recommended. It encourages relaxation of the caution and vigilance that have been wisely adopted as a result of bitter experience in the past with prolonged steroid therapy. It restricts flexibility and encumbers adjustment of dosage of the separate ingredients to the individual needs of the patient.

The limits of this paper will not permit a review of the results obtained with steroid therapy in the several rheumatic diseases. An abundant literature on this subject, including many reviews, has accumulated since Hench and his associates published their historic observation in 1949. There is a wide range of opinions on the value of steroid therapy in rheumatoid arthritis, rheumatic carditis, systemic lupus erythematosus, polyarteritis nodosa, systemic scleroderma and dermatomyositis. We believe that steroids have an important place in the treatment of certain types of cases in each of the diseases mentioned.

Hazards of Prolonged Steroid Therapy

The undesirable side-effects in prolonged steroid administration are numerous and known well enough not to require repetition h
In a recent report Howell and Ragan[21] listed 41 different untoward effects observed in 68 patients with rheumatoid arthritis given prolonged hormonal therapy and observed for a period of five years. The aggregate number of adverse events in the 68 patients was 404. In general, the vast majority of undesirable symptoms, however, are of minor importance clinically and certainly do not indicate need for interrupting therapy.

Four major side-effects—peptic ulcer, compression fracture, mental disturbance and collagen-vascular disease—require special consideration because they occur not uncommonly, are disabling, and may be of serious consequence.

Peptic Ulcer

It has been estimated that in the general population 5 to 10 per cent develop a peptic ulcer during a lifetime, whereas at any one annual survey the prevalence will vary from one to three per cent.[22] In England peptic ulcers have been reported to occur in 5.8 per cent of men and 1.9 per cent of women between ages 15 and 64.[23] In two arthritis clinics the frequency of peptic ulcer among patients with rheumatoid arthritis who had not received steroid therapy was 4.5 and 8.0 per cent.[24a, b] In our series of 64 patients treated with cortisone for 6 to 42 months, the incidence of peptic ulcers was 8 per cent.[25] In Ragan's series of 68 patients observed for a similar period the incidence was 26 per cent. In a group of 15 patients treated with prednisone or prednisolone and observed by us for 12 to 24 months, the incidence was 27 per cent (four patients). Each of the four patients who developed an ulcer received 20 mg. or more of prednisone daily. Kern, Clark and Lukens[24c] found that 3 of 14 (21 per cent) prednisone-treated patients developed peptic ulcer when the daily dose was 20 mg. or greater, whereas none of 54 patients developed ulcers when the daily dose was held to 15 mg. or less. Boland[18] reported an ulcer incidence of only 6.5 per cent in a group of 141 patients with rheumatoid arthritis treated with prednisone or prednisolone for six to nine months. The short period of observation and lower dosage may account in part for the discrepancy between 27 per cent in our series and 6.5 per cent in Boland's. It is noteworthy that the incidence of gastric complaints simulating those that accompany peptic ulcer increased from 5.5 per cent to 31 per cent when 109 of Boland's cases were transferred from hydrocortisone to prednisone therapy.

Ulcers may appear during the first few weeks of steroid administration or not until the second or third year. Although there is no apparent relation to duration of therapy, there does seem to be a direct relation to size of daily dose.[24c] Ulcers may occur in the stomach or duodenum. They often heal during continued steroid therapy when conventional ulcer management is instituted (diet, antacids and anticholinergic drugs). On the other hand, some may perforate or bleed severely without warning or even without antecedent symptoms. The outcome may be fatal. Of 11 deaths in Ragan's series, two were due to bleeding peptic ulcer and one to perforation.[21] In view of these potential hazards it may be prudent to prescribe antacids and an ulcer

regimen prophylactically when steroid therapy is first instituted. The most promising means of reducing the risk of ulcer is to reduce the size of daily dose of steroid to 50 mg. of cortisone or 15 mg. of prednisone or less.

Osteoporosis and Compressed Fractures

Osteoporosis occurs commonly in active rheumatoid arthritis and increases with severity and duration of the disease even when the patient is treated with conservative measures. Nevertheless, the incidence of compressed fractures of the vertebrae (and to a lesser extent of other bones) is apparently greater in patients given prolonged steroid therapy. Furthermore fractures have been observed in steroid-treated patients with diseases other than rheumatoid arthritis, diseases not otherwise associated with vertebral compression.

Of 59 patients with rheumatoid arthritis receiving long-term cortisone therapy and observed for four years, fractures occurred in seven per cent.[25] Of 15 patients with the same disease given prednisone and observed for one to two years, fractures occurred in five (33 per cent).[26] Four of these prednisone-treated patients had previously received long-term cortisone therapy but only one had suffered a fracture while taking cortisone. One of the five patients was a male; one female patient was 28 years old and the other three were at or past the menopause. All patients were ambulatory and were engaged in normal activity when fracture occurred.

The commonest sites of fracture are in the dorsal or lumbar vertebral bodies. As a rule, the anterior vertebral border is compressed and neurological complications do not occur. At the onset, back pain is usually but not invariably present and it generally disappears in a few days or weeks. In most cases it is not necessary to discontinue steroid administration.

The mechanism for this deleterious effect is not entirely clear. Similarity between the occurrence of this manifestation in induced hyperadrenalism and in naturally-occurring Cushing's syndrome is striking, the incidence of osteoporosis in the latter condition having been reported as 24 patients of 29 in one series[27] and 10 of 17 in another.[28] The best explanation thus far advanced is based on Albright's doctrine that osteoporosis is a disease of protein matrix of bone and not of bone itself. The adrenal oxysteroids, being anti-anabolic, interfere with the process of matrix formation while bone resorption pro-

ceeds at a normal rate. Administration of these steroids causes an increase in urinary nitrogen excretion and, unless protein intake is high, negative nitrogen balance.[29] Calcium balance studies have been relatively few and thus far have not demonstrated consistently significant calcium loss or negative balance. Additional studies are needed to elucidate the full explanation for osteoporosis associated with steroid therapy.

The effectiveness of estrogen and androgen in protecting the skeleton during cortisone therapy has been studied by Henneman and his associates,[30] in patients with intractable asthma. Measuring only urinary calcium excretion, these workers found that the sex steroids reduced to normal the urinary calcium excretion of patients with hypercalciuria but were without effect in patients with normal urinary calcium excretion. To date the reported results of androgenic and estrogenic therapy in reducing the hazard of fracture have not been impressive. The efficacy of the sex steroids and also of dietary calcium in protecting the skeleton during hormonal therapy is currently under study by Dr. Whedon of our Institute who is employing the complete balance technique.

Mental Disturbances

After a thorough review of the literature and a scholarly analysis of the many hypotheses advanced to explain the causality of mental disturbances associated with corticotropin and cortisone administration, Quarton and associates[31] concluded that our knowledge on this subject is inadequate, the mechanism of these disturbances not well understood, and a completely satisfactory hypothesis has not yet been formulated. It was assumed that hormonal therapy might inconstantly produce in susceptible patients a specific pattern of altered function of the nervous system. This change could result from the interaction of several factors both internal and environmental, such as central vascular lesions (present in cases of systemic lupus erythematosus), certain metabolic and endocrine disorders, emotional stability of the individual, and situational factors which bear on the psychological defenses of the patient.

Goolker and Schein[32] conducted a detailed study of the psychic effects of corticotropin and cortisone in 80 patients with diverse diseases including systemic lupus erythematosus, asthma, rheumatoid arthritis, rheumatic fever and blood dyscrasias. Fifteen per cent exhibited distinct aberrant psychic reactions that were mostly transitory and mild. The

patterns observed were classified as depressions, paranoid reactions, and schizophrenic and toxic syndromes. The reactions were not predictable since no consistent relation could be detected between the incidence or type of aberration and the size of dose, duration of therapy, associated metabolic alteration or even pre-treatment psychic state. Glaser[33] found that the pre-treatment personality pattern determined the psychological content of the psychosis but not its onset. The relationship between electroencephalographic changes and psychotic reactions was not consistent. The reported incidence of psychosis has ranged from 0 to 10 per cent[21] and averaged about 5 per cent.[33] It is interesting that the manifestations of the somatic disease are usually suppressed during psychosis even after hormonal therapy is interrupted.

Whether steroid should be discontinued when mental disturbances supervene will depend on the severity and nature of the reaction. As mentioned, in most cases the aberration is benign and self-limited. In other cases electroconvulsive therapy may be necessary. The hazard of suicide in the depressive reactions and of protracted psychosis requires assessment when continuance of hormone therapy is contemplated.

Collagen-Vascular Disease
(Systemic lupus erythematosus, polyarteritis nodosa)

In the past year we observed three patients among 29 with rheumatoid arthritis who developed polyarteritis nodosa and one patient with diffuse scleroderma (confirmed by skin biopsy) who developed clinical features of systemic lupus erythematosus while receiving prolonged prednisone therapy. Since pre-treatment biopsies were not done on the rheumatoid patients it is difficult to be certain that vasculitis had not been present before steroid administration was begun. In the case of scleroderma, however, tests for L.E. cells were negative before prednisone was given and became positive after 15 months of treatment, when the dose was being reduced. Slocumb[34] drew attention to the occurrence of "transitory panmesenchymal reactions" in patients with rheumatoid arthritis when cortisone was gradually withdrawn following signs of "hypercortisonism." He noted L.E. cells in 15 patients and polyarteritis in three. Such reactions were seen by Slocumb only in patients with rheumatoid arthritis. Other workers have reported similar findings in rheumatoid patients whose cortisone was either being maintained or had been recently discontinued.[35-38]

It should be emphasized, however, that before the advent of corti-

sone, arteritis was recognized as an integral part of the pathological changes encountered in rheumatoid arthritis.[37] This finding has since been confirmed by others.[39-40] It is now apparent that the severity of the vasculitis may range from very mild arteritis to necrotizing angiitis indistinguishable from that seen in polyarteritis nodosa. Several workers have reported the presence of this lesion in patients with rheumatoid arthritis who had not received steroid therapy.[36, 37, 41-43]

Arthritis commonly appears among the earliest manifestations of systemic lupus erythematosus and not infrequently may be the only clinical expression of the disease for several years before the typical features of systemic lupus erythematosus supervene. In such cases the joint changes are often indistinguishable from rheumatoid arthritis.[44, 45]

Statistically valid studies on the incidence of collagen-vascular disease in comparable groups of patients with rheumatoid arthritis treated and untreated with steroids have not yet been reported. Further investigation is required to clarify the role of steroid administration in the pathogenesis of necrotizing vasculitis or systemic lupus erythematosus in patients with rheumatoid arthritis.

When these complications develop it is reasonable to resume or continue steroid therapy since this is the drug of choice in the treatment of spontaneously occurring collagen-vascular disease. When the patient improves, attempts may then be made to gradually discontinue the drug. The response of these complications to steroid therapy will vary with their severity. In fulminating cases the outcome is often fatal.

Summary

With the aid of radioactive hydrocortisone, the rate of endogenous synthesis of hydrocortisone, the size of its miscible pool, the rate of its absorption, metabolism and excretion in man have been measured.

Synthetic antirheumatic steroids have certain advantages in contrast to cortisone and hydrocortisone but share with the latter important limitations and serious, adverse effects, some of which may be fatal. The risk of deleterious side-effects can best be reduced by reducing the size of the daily dose of steroid. The need for cautious and circumspective selection of patients is imperative. The expected beneficial results from steroid therapy and the hazard of withholding treatment should outweigh the risk of serious adverse effects.

Despite their limitations and hazards, the 11, 17-oxygenated steroids occupy an important position in the treatment of selected cases of each

of the rheumatic diseases mentioned and may prove to be life-saving.

New steroids are currently being synthesized and tested with the objective of finding a steroid that will be free of serious side-effects yet retain anti-inflammatory potency.

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